

Worldwide Development
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July 28, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. [2004D-0187]: "Draft Guidance for Industry on Premarketing Risk Assessment" (69 Federal Register 25130; May 5, 2004)

Dear Sir/Madam:

The following comments on the above-captioned *Draft Guidance for Industry on Premarketing Risk Assessment* (Draft Guidance) are submitted on behalf of Pfizer Inc. Pfizer discovers, develops, manufactures, and markets leading prescription medicines for humans and animals and many of the world's best-known consumer brands. Our innovative, value-added products improve the quality of life of people around the world and help them enjoy longer, healthier, and more productive lives. The company has three business segments: health care, animal health and consumer health care. Our products are available in more than 150 countries.

Pfizer is committed to provide access to safe and effective medicines. As a consequence, we have made a major commitment to Risk Management for the safety of our products. The cornerstone of our approach is to understand the unique characteristics of each product and implement relevant Risk Management strategies in ways that improve patient benefit without unreasonably restricting access. Further, we support incorporation of Risk Management concepts early in the product development cycle as part of a continuum in the assessment of benefit-risk for each product. The Draft Guidance, one of three on Risk Management activities¹, provides guidance on good risk assessment practices during the pre-marketing phase of the drug development process. When finalized, we anticipate that the guidance will help provide transparency of the Agency's policies and expectations regarding this important aspect of drug

¹ The Draft Guidance is a companion document to two others: *Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans* (Docket No. 2004D-0188; 69 Federal Register 25130; May 5, 2004) and *Draft Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (Docket No. 2004D-0189; 69 Federal Register 25130; May 5, 2004). Each of the three documents, developed to meet FDA's PDUFA III Performance Goals, was preceded by a draft Concept Paper and these papers were discussed at Public Workshops on April 9-11, 2003 (Docket 02N-0528; 68 Federal Register 11120, March 7, 2003, and 68 Federal Register 25049, May 9, 2003).

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development. We commend the Agency for actively engaging stakeholders in the development of this guidance and for considering our earlier comments. Indeed, we strongly endorse the use of Concept Papers¹ by FDA to facilitate early dialogue on important issues and we encourage FDA to continue this practice in the future. We appreciate the present opportunity to provide new comments and reinforce some of our previous comments on premarketing risk assessment.

We consider the Draft Guidance to be a significant improvement over the Concept Paper as a result of our input and that of other stakeholders. Indeed, Pfizer agrees with and supports most of the concepts outlined in the Draft Guidance, particularly the overarching philosophy that the ultimate goal of Risk Management is to ensure effective processes for minimizing risk while preserving benefits of medical products. We agree that this is an iterative process that should occur over the entire lifecycle of a product, with differences in intensity based on accrued experience, and, because all risk cannot be predicted with certainty, safety evaluations may need to be refined as experience with the product evolves. We also agree with the statement that, "Many recommendations in this guidance are *not* intended to be generally applicable to all products."

We believe that Risk Management activities are a shared responsibility and should encompass a worldwide perspective. Thus, we endorse FDA's participation in Industry-Regulator consensus forums, such as the International Conference on Harmonization (ICH) and the Council for International Organizations of Medical Sciences (CIOMS), to maintain global consistency and harmonization on this important topic. The Draft Guidance includes a non-specific statement regarding international harmonization, with the completed ICH E1A and E3 guidelines given as examples. However, relevant and important international consensus work is ongoing, e.g., activities of the ICH E2E Expert Working Group (Pharmacovigilance Planning) and the CIOMS VI Working Group (Managing Safety Information from Clinical Trials of Medicinal Products); the work products of these groups are scheduled to be finalized in the near future. Therefore, we strongly urge FDA to fully consider the final ICH and CIOMS consensus documents before finalizing the guidance on premarketing risk assessment.² If any divergence from consensus agreements were contemplated, it would be important for FDA to provide the rationale for the divergence and also an FDA proposal for eventual international harmonization.

Despite broad agreement with the Draft Guidance and its companion documents¹, we have identified several areas that we would like to reinforce as FDA contemplates final guidance. Our general comments on these areas are:

- **International harmonization provides advantages.** Risk Management is a shared global responsibility and stakeholders should endeavor to avoid multiple strategies merely to serve local needs, which could result in fragmented Risk Management for a given product (NB: Within a harmonized

² FDA published notice of availability of ICH E2E draft guidance (Pharmacovigilance Planning) on March 30, 2004 (69 Federal Register 16579); the ICH consensus process on this topic will result in a final guidance (ICH Step 4) in November 2004 at the earliest. The CIOMS VI Working Group plans to make their report available in late 2004 or early 2005. The FDA Performance Goals associated with PDUFA III indicate that final guidance for pre-marketing risk assessment will issue by October 2004, before the international consensus documents are available.

approach, however, there should be enough built-in flexibility to accommodate the real needs of individual products and individual countries). To further this, care should be taken to incorporate consensus definitions and approaches, e.g., those developed by ICH and CIOMS, wherever possible to ensure the most efficient use of resources by Industry and by Regulators. Please see the point above regarding related documents and the timing of their availability;

- **Consistency in terminology and its use are critical.** To maximize the benefits of Risk Management, it is important to have clear terminology and definitions and to use these terms consistently. This should be done at the global level and also within and across FDA guidance documents. We note several inconsistencies within the Draft Guidance and companion documents. For example, the term "signal" is used with different meanings. Also, the terms "Risk Minimization Action Plan" ("RiskMAP") and "Pharmacovigilance Plan" ("PVP") are not used consistently across the three guidances. It is important to clarify in final guidance that a RiskMAP is reserved for selected occasions; the definition of a PVP and the use of this term should be aligned with the nascent ICH agreement. Another example is "Pharmacovigilance Scope," which seems to be used throughout the text with a narrower definition than the definition that was initially provided. We suggest that the Agency review terminology in the documents for clarity and consistency;
- **Stakeholder dialogue is essential.** The use of Concept Papers and Public Workshops was welcome in this case and is a practice that should be continued by FDA when introducing important guidance. This encourages early involvement of stakeholders and we believe that it serves to enhance transparency and will improve the desired public health outcome. In the case of the Draft Guidance, we believe that relevant stakeholders should be involved in both the development of guidance and in the planning and implementation of actions for situations when a product may pose an unusual type or level of risk. Mechanisms should be established to ensure (a) dialogue between the Agency, Sponsor, and others, when appropriate, and (b) interaction within the Agency, e.g., Reviewing Divisions and the Office of Drug Safety. We believe that it would be appropriate to establish a schedule of opportunities for dialogue at various stages of a product's lifecycle. Collaborative discussion of strategy and interpretation of data should result in a common understanding of relevant issues. We believe that this will provide a platform for constructive interactions in the best interest of the public health and will minimize misunderstandings. Further, it should be emphasized that all data sources should be considered - no single source of data should be used in isolation;
- **Risk Management is a continuum.** We believe, along with FDA, that the concept of Risk Management should begin early in product development and evolve at each phase of development as additional information is accumulated. However, all products are not the same and the need for Risk Management activities should be considered on a product-by-product basis;
- **Consensus must be reached on tools and it must be acknowledged that novel tools may emerge.** Simplicity and flexibility are the cornerstones of appropriate tools. We agree with the statement in the Federal Register notice (69 Federal Register 25131; May 5, 2004) that sponsors should, "give every consideration to using the least burdensome method to achieve the desired

public health outcome.” This should be re-stated in all three guidance documents. Tools must be considered on a case-by-case basis, and agreed between the agency and the sponsor as appropriate. Because Risk Management is an evolving field, novel tools may be developed in response to a specific need. Further, a clear distinction should be made between tools that should be used to characterize risk versus those that can be applied to manage risk. For example, a case control study that is conducted as part of a Post-Approval Commitment may be useful to learn more about a certain risk, but such a study should not be considered useful as a tool to *manage* risk;

- **A uniform approach to labeling is needed.** Prescribing Information should be evidence-based and standardized where possible, e.g., agreement should be reached on what information goes into each section of product labeling and standard criteria should be developed for **bolded**, *italicized*, and black box wording. We believe that this would facilitate product comparisons by prescribers;
- **Individual willingness to accept risk should be considered when balancing benefit with risk.** Allowance for individual variability in willingness to accept risk, whether due to the nature of the underlying illness or the nature of the individual patient, should be considered in reaching a final decision on approvability of a product for marketing. The approach in the Draft Guidance is primarily population-based rather than patient-based and, although we understand FDA’s role and interest in the public health, we feel a strictly population-based approach could unnecessarily restrict access to certain medications; and
- **Good Guidance Practices are encouraged.** The Agency’s expectations should be tied directly to FDA’s current legal authority to regulate the safety of drugs. Namely, FDA’s expectations for regulated companies’ Risk Management activities should be tied directly – and exclusively – to whether these activities help to ensure that marketed drug and biologic products are safe; these activities should avoid redundant or ineffective activities, and should not set different standards from those expressed in other guidance documents, e.g., size of safety database.

In addition, we would like to emphasize the following point:

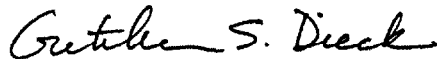
- **Comparisons of newer products to established ones can be misleading.** The discussion regarding the comparison of the “advantages” of a new product to established products (Draft Guidance, line 155) is worrisome for at least five reasons: (a) It implies that newer products might be held to higher standards than comparators, (b) It invites newer products to be considered “therapeutically equivalent” to established ones, i.e., the clinical impact is viewed as being the same for different molecular entities, which has the effect of restricting access to the newer product, (c) It may create a false impression that one knows all the “potential” advantages of a new product, particularly at the time a product enters the marketplace, (d) It may involve comparison to older products that may not have received sufficient scrutiny to determine their true characteristics, positive and negative, and (e) It may overlook patients who cannot tolerate or who do not receive benefit from the comparators. We suggest that FDA consider adding such cautions in final guidance.

In summary, Pfizer endorses the thoughtful use of Risk Management concepts and practices throughout the continuum of a product's lifecycle, i.e., during the pre-approval, peri-approval, and post-marketing phases of product development. We believe that dialogue among stakeholders is key and we view Risk Management as a global process. In addition to population-based approaches, we place high importance on individual willingness to accept risk, whether due to the nature of the underlying illness or the nature of the individual patient, and this should be considered when making decisions regarding access to a given product. Harmonization of definitions, terminology, format, and tools will enable companies to use the same basic Risk Management Plan worldwide and enhance harmonization of Risk Management approaches around the globe for a specific product. We encourage FDA to strive for consistency with the relevant consensus documents from ICH and CIOMS, which may delay FDA's publication of final guidance because the consensus documents will not be available until after the PDUFA III Performance Goals date for the guidances.

Finally, we support comments made by the Pharmaceutical Research and Manufacturers Association (PhRMA) at the Public Workshops and we also support PhRMA's written comments to Docket 02N-0528 and Docket 2004D-0187. We thank FDA for the opportunity to comment on this important topic and we would be pleased to respond to any questions that the Agency might have.

Our specific comments on the Draft Guidance are attached.

Sincerely,

A handwritten signature in black ink, appearing to read "Gretchen S. Dieck". The signature is fluid and cursive, with the first name being the most prominent.

Gretchen S. Dieck

cc: <http://www.fda.gov/dockets/ecomments>

I. Specific Comments

Premarketing Risk Assessment (Docket 2004D-0187)

These comments apply to the FDA Draft Guidance titled "Premarketing Risk Assessment," dated May 2004. Comments are arranged in bullets that include line references to the Draft Guidance where appropriate.

The need for flexibility of Risk Management from product to product is emphasized in the Draft Guidance and we acknowledge that FDA has addressed many of our previous specific comments. We have some lingering concerns in several areas:

- Beginning with line 143, there is a discussion of "Size of the Premarketing Database"; we commented on this extensively in our previous comments and still believe these comments to be important. One point from our prior comments that we wish to stress is that expansion of a premarketing database is not likely to result in detection of rare events. Carefully constructed post-marketing safety surveillance is a better approach to detect rare events in the perspective of actual product use. This point is illustrated by the following table, which illustrates the probability of finding one event (3rd column) or two similar events (4th column). For example, in order to find two events (one initial, one confirmatory) at the one in 10,000 rate, a database of 20,000 patients on the investigational drug would only provide about a one in two chance of detection, with about a 15% chance that the event would go entirely unobserved.

Event rate	Sample size	Probability (at least 1 event)	Probability (at least 2 events)
1%	500	0.993	0.960
0.5%	500	0.918	0.713
	1,000	0.993	0.960
0.1%	1,500	0.777	0.442
	3,000	0.950	0.801
0.01%	6,000	0.451	0.122
	10,000	0.632	0.264
	20,000	0.865	0.594

- The discussion in line 194 that increasing the number of patients to define adverse events related to time of exposure is not logical because this would only be achieved by extending duration of exposure.
- Considering lines 250ff, there are practical and ethical constraints on conducting long-term controlled clinical trials. It would rarely, if ever, be ethical to conduct placebo-controlled safety studies in any indication where there is a standard of care or active comparator with a morbidity or mortality benefit. In addition, particularly in long-term trials, differential drop-out rates can make imputation of missing safety data very difficult and potentially misleading. If two adequate and well-controlled studies were conducted against an active comparator, with pre-specified research objectives and hypotheses and the results of the studies support the hypothesis, relative safety claims (whether the claims are on

superiority or non-inferiority) should be allowed. This would be in the context of performing these studies for specific hypothesis testing, with agreed *a priori* endpoints and outcomes, as is done for efficacy studies.

- Although studying doses in Phase 3 that are higher than those ultimately recommended may add to the safety database, this should not be done solely for this purpose. Phase 2 studies should rule out poorly tolerated and suboptimal doses, and doses studied in Phase 3 that are ultimately not used will have been extensively studied on the assumption that they could be labeled doses and only subsequently determined to be inappropriate. This scenario is generally to be avoided, as sub-optimal doses would ideally not be used beyond Phase 2 because the use of suboptimal doses would not be expected to provide a benefit. At the end of Phase II, only those doses that appear to have potential to be the labeled doses should be carried forward into the Phase III program.
- Regarding comments on product disease interactions in lines 342-343, there should be sufficient variability in and prevalence of concomitant diseases within the intended final population to provide relevant information.
- The bullet in lines 382-385 should be deleted because it inhibits innovation by raising the bar for new products.
- Large Simple Safety Studies (LSSS) are discussed beginning in line 443, and it is still unclear what is the appropriate frequency of rare adverse events to identify. Despite their large size, such studies are still not large enough to determine risk factors around very rare events where routine post-marketing surveillance would be a more effective tool. Such studies are limited by need to know the dose(s) that have demonstrated favorable benefit/risk information and substantial knowledge of the safety profile. Therefore, conduct of a LSSS may be most appropriate as a Phase IV commitment as part of the ongoing approach to ascertain risk. In the pre-approval setting, LSSS are probably best used when there are specific events (perhaps identified safety signals) which are discernable in Phase II and no other Phase III approach seems adequate to explore such signals.
- Minimization of preventable medication errors (lines 475ff) is difficult during the premarketing phase as currently carried out because the information required is not readily available and the medication use setting is so much more controlled.
- Regarding grouping of dictionary terms as described in Lines 642ff, clarity is needed as to the best timing for this discussion between the sponsor and agency, and it should be done in the context of available strategies for group terms and of coding conventions.
- Lines 789-797 of the guidance still states that, when the results of a pooled analysis show a diminished statistical association and/or less risk compared to the safety signal originally obtained from one or more of the contributing clinical trials, it could suggest inappropriate use of data pooling. We do not agree with this cautionary statement. While we agree that pooling should be based on sound scientific rationale, when more data are pooled based on pre-specified principles, the previously observed event rates could go up or down due to sampling fluctuations. The fact that a particular rate goes down after more data become available does not necessarily imply the loss of sensitivity or inappropriate pooling as long as the pre-specified pooling strategies are followed. This is especially true if an earlier high-observed rate was a result of observing one or two events in a small sample. We continue to suggest that FDA reiterate the importance of an appropriate predefined pooling strategy.

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- Lines 920-925 refer to collection of medical records relating to adverse events and making them a part of the Case Record Form. The scientific arguments presented are compelling, yet difficult to achieve in the current healthcare environment, be it here in the US or elsewhere in the world due to personal medical data privacy concerns and compliance with local existing law.